Pretreatment Predictors Associated with Improvement in Hepatitis C virus Related Decompensated Cirrhosis After Direct-Acting Antiviral Therapy

Abstract

Background &Aim: The availability of hepatitis C virus (HCV) direct-acting antivirals (DAAs) has led to a paradigm change in the care of HCV related decompensated cirrhosis. Achieving a stained virologic response (SVR) is associated with considerable improvements in both Child-Turcotte- Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores in decompensated cirrhosis**.** We aimed to evaluate the pretreatment predictors associated with improvement in CTP B cirrhosis after DAAs and evaluate the efficacy and safety of DAAs in these patients**. Patients and methods:** A prospective study conducted on 213 decompensated patients (CTP B, 134 received DAAs for 24 weeks and 79 for 12 weeks). Clinical and laboratory data obtained at baseline, during treatment, 12 weeks after end of treatment (EOT), 36 weeks after treatment start, and 24 weeks after SVR. **Results:** We had 48.4 % and 55.9 % had improved to CTP A at 36 weeks of treatment start and 24 weeks after SVR respectively. A high baseline BE3A score (which includes Body mass index (BMI), Encephalopathy, Ascites, Alanine aminotransferase (ALT) and Albumin) was the significant predictor of attaining CTP A at 36 weeks of treatment start, while high baseline ALT (> 60 IU/L) was the significant predictor of attaining CTP A at 24 weeks after SVR. SVR 12 achieved in 97.3% and DAAs were safe with mild tolerable adverse events. **Conclusion:** High baseline ALT and BE3A score were the significant predictors of hepatic improvement from CTP B to CTP A after DAAs. HCV DAAs were safe and effective with high SVR rates (97.33%).

Keywords: Hepatitis c virus, Decompensated cirrhosis, Direct acting antivirals, Child Turcotte- Pugh score.

Introduction:

Globally, there were an estimated 56.8 million viremic HCV infections at the start of 2020 which was down from an earlier estimate in 2015 [1]**.** The prevalence of HCV positive antibody is reported to be 10% and HCV positive RNA of 7% in the 15–59-year-old age group by Egyptian Health Issues Survey 2015 [2]**.** In Egypt, chronic HCV infection is the leading cause of liver cirrhosis so, Egypt's national program seeks to treat more than 250,000 chronic HCV infected persons per year to decrease the prevalence of chronic infection to less than 2% by 2025 and less than 1% by 2030 [3]**.**

Chronic HCV infection affects about 55–85% of individuals with 15–30% developing cirrhosis after 20–25 years of HCV infection. The probability of progression to hepatic decompensation is about 3-6% per year [4]**.** Previously, the only treatment option for

decompensated cirrhotic patients was LT, but the availability of HCV DAAs has led to a paradigm change in the care of HCV related decompensated cirrhosis [5]**.** HCV treatment is now recommended in HCV decompensated cirrhosis due to the availability of SOF-based combination DAAs with daclatasvir (DAC) or ledipasvir (LDV) or velpatasvir (VEL) with or without ribavirin (RBV)**.** The primary goal of HCV treatment is to achieve SVR which is defined as a negative HCV ribonucleic acid (RNA) 12 weeks after DAAs stoppage [6]**.**

SVR rates were lower in patients with decompensated cirrhosis than in patients with compensated cirrhosis, which several studies explained by altered DAAs metabolism, reduced drug delivery by shunting, and altered DAAs uptake due to more compromised hepatic synthetic function in late CTP B & CTP C [7, 8]**.** SVR is associated with considerable improvements in CTP and MELD scores, such that certain patients may be withdrawn from the LT waiting list and eventually delisted [6, 9]**.**

The decision to treat HCV related decompensated cirrhosis by DAAs is based on assessing the benefits and risks of treatment so, *El-Sherif et al.* had studied a new score (BE3A) and concluded that Patients with a high BE3A score had a chance of improvement toward compensated cirrhosis. BE3A score composed of the sum of five factors (body mass index (BMI) < 25 kg/m ^{2}, absence of encephalopathy, absence of ascites, alanine transaminase (ALT) > 60 IU/l, and albumin > 3.5 g/dl), it was calculated by simple numerical summation of its components, where 1 point was assigned for each component [10]**.** There are few studies regarding predictive factors of clinically treatment benefit of DAAs in decompensated HCV-related cirrhosis. So, we aimed to detect pretreatment factors of hepatic re-compensation in CTP B cirrhosis and to evaluate the efficacy and safety of HCV DAAs in these patients.

Materials and methods:

In this prospective study, a total 286 decompensated patients were recruited for HCV treatment at the Viral Hepatitis Treatment Unit in Tanta University Hospital and National Liver Institute in Menoufia University. Of these, 40 patients were excluded, and 246 patients were enrolled and received HCV DAAs. Only 213 from 246 patients completed to the end of the study. The study started from April 2019 to April 2021 under the supervision of National committee for control of Viral Hepatitis (NCCVH).

Inclusion criteria: Chronic HCV with positive HCV RNA, HCV treatment-naïve, aged more than 18 years and CTP B cirrhosis in which diagnosis of cirrhosis based on, history taking, clinical and radiological examination, and laboratory tests.

Exclusion criteria: Decompensated cirrhosis (CTP B9 & CTP C), pregnant females, HCC except 6-12 months after curative intervention, extra-hepatic malignancy except after 2 years of disease-free interval except in cases of lymphomas and chronic lymphocytic leukemia, HBV or HIV co-infection, platelets <50,000/mm^3, hemoglobin < 10 gm/dl, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 5 ULN were the exclusion criteria according to NCCVH protocol.

Methods: Full history taking, clinical and radiological examination (liver ultrasound and triphasic abdominal computerized tomography if indicated), ECG in patient > 65 years or cardiac patient) and upper GI endoscopy before starting treatment for most of patients. Baseline laboratory investigation: included complete blood count, liver functions (albumin, bilirubin, ALT, aspartate transaminase (AST) & international normalized ratio (INR), serum creatinine, fasting blood sugar, serum alpha-fetoprotein, HCV antibodies by ELISA, polymerase chain reaction for HCV, Hepatitis B surface antigen, Hepatitis B core antibody, human immune deficiency virus antibody, pregnancy test in female patients in childbearing period and BMI with estimation of dry body weight in (ascitic or who had pedal edema) by subtracting 5% in mild ascites and 5% in bilateral pedal edema [11]**.** Three baseline scores were calculated as CTP, MELD and BE3A scores through web-based calculators.

Treatment regimens which used were SOF (400mg) + DAC (60mg) for 24 weeks, SOF/ LDV (400 mg / 90 mg) for 24weeks, SOF/ VEL (400 mg / 100 mg) for 24 weeks and SOF + DAC + RBV for 12 weeks and SOF/ LDV+ RBV for 12 weeks. RBV was received by initial starting dose 600 mg and gradually increased at a dose of 200 mg/week to the maximum 1000 mg if tolerated. RBV dose was decreased when Hb decreased by 2 gram or became less than 10g/dl and stopped when Hb became less than 8.5 g/dl. RBV was not used in those whose baseline Hb was < 10 g/dl, in those with depression or in cardiac dysfunction.

Follow up: To assess safety and efficacy of DAAs every 2 weeks in patients who received DAAs plus RBV and monthly in patients who received DAAs without RBV, at 12 weeks after end of treatment (EOT), at 36 weeks of treatment start and at 24 weeks after SVR.

Study outcomes: Primary study outcomes**,** detection of the proportion of compensated CTP class A patients after DAAs at 24 weeks after SVR. Secondary study outcomes**:** SVR12 rate which is defined as HCV RNA is less than the detection limit 12 weeks after EOT.

Study endpoints: Primary end point was follow-up patients until 24 weeks after SVR. Any serious adverse events that lead to discontinuation of treatment or development of HCC and /or death were secondary end points.

Statistical analysis: Data analysis was performed using SPSS version 20 (Statistical Package for Social science) for Windows. Quantitative data were presented as mean ± standard deviation (SD). Qualitative data was presented in the form of s numbers (%). Chi square test (X2 value) was used to compare a qualitative variable between two independent groups or more. Logistic regression analysis for odd ratio (OR) was used. P value was calculated either non-significant if > 0.05, significant if ≤ 0.05, or highly significant if < 0.001).

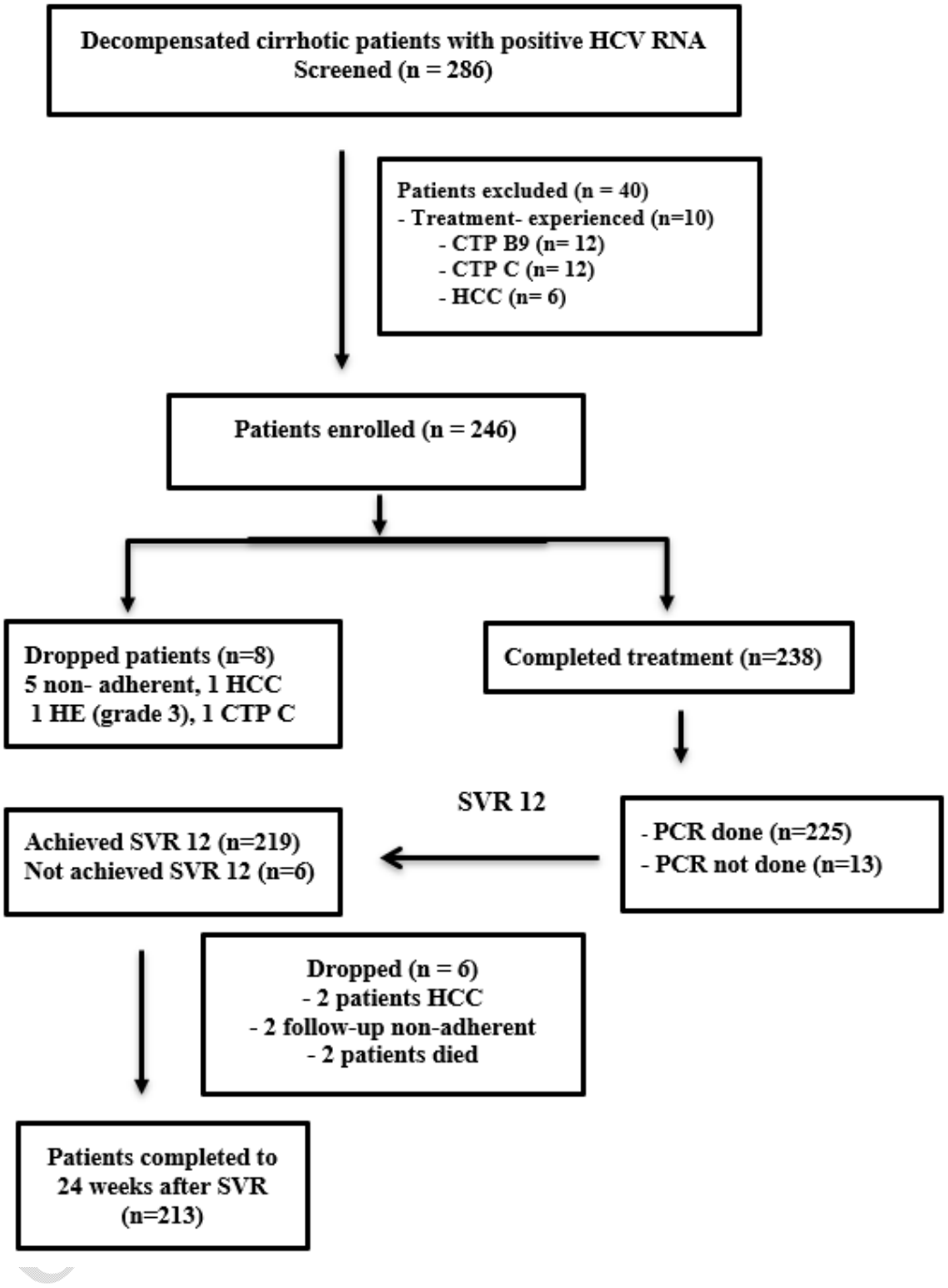

Figure (1): Flow chart of patients screening in the study. CTP = Child-Turcotte- Pugh, HCV= hepatitis C virus, HCC= hepatocellular carcinoma, SVR= sustained virologic response, PCR= polymerase chain reaction.

Results:

Demographic and clinical characteristics of the study population: In total, 286 HCV related decompensated patients were screened, 40 were excluded and 246 patients were enrolled and received HCV DAAs. SVR 12 was achieved in 219 patients (97.33%). Finally, 213 patients completed to end of study and statistical analysis was done for this number with mean age 56.07 ± 7.04, 53.5% were females and 46.5 % were males, about 58 (27.2 %) patients had mild ascites, 115 (53.9%) patients had lower limb edema, 11 (5.16%) had tinge jaundice, 4 (1.88%) had history of hepatic encephalopathy (grade 1-2). Grade I varices were detected in 34 patients (18.38%), grade II varices were detected in 71 patients (38.38%), grade III varices were detected in 45 patients (24.32%) & grade IV were detected in 20 patients (10.81 %).

Baseline BE3A score ranged from (1- 4), BE3A score 1in (19.3%) 41 patients, BE3A score 2 in 69 (32.4%) patients, BE3A score 3 in 82 (38.5%) patients had & BE3A score 4 in 21 (9.9%) patients. Treatment regimens: included SOF (400mg) + DAC (60mg) for 24 weeks in 111 (52.11%) patients, SOF/ LDV (400 mg / 90 mg) for 24weeks 18 (8.45%), SOF/ VEL (400 mg / 100 mg) for 24weeks in 5 (2.35%) patients), SOF + DAC + RBV for 12 weeks in 74 (34.74%) and SOF/ LDV+ RBV for 12 weeks 5 (2.35%) patients) **(Table 1).**

Follow–up during DAAs: There was a highly significant decrease in ALT& AST and a significant increase in platelet count during DAAs until EOT. There was a highly significant increase in serum bilirubin mainly indirect bilirubin and a significant decrease in hemoglobin (Hb) during DAAs plus RBV until EOT **(Table 2& 3).**

Table (1): Demographic and baseline characteristics (n=213)

Parameters	Value
Age	56.07 ± 7.04
Gender	
Female	114 (53.5%)
Male	99 (46.5%)
BMI	
Mean ± SD	29.35 ± 4.27
BMI<25	24 (11.3%)
BMI 25-30	108 (50.7%)
BMI >30	81(38%)
Jaundice	
No	202(94.8%)
Yes	11 (5.2%)
Lower limb edema	
No	98 (46%)
Yes (on diuretics)	115 (54%)
Ascites	
No	155 (72.8%)
Yes (on diuretics)	58 (27.2%)
Hepatic encephalopathy (HE)	
No	209 (98.12%)
grades 1, 2	4 (1.9%)
Presence of varices	
No varices	15 (8.1%)
Grade I	34 (18.38%)
Grade II	71 (38.38%)
Grade III	45 (24.32%)
Grade IV	20 (10.81%)
Creatinine	0.82 ± 0.02
Fasting blood sugar	143.4 ± 66
HCV RNA (IU/ml)	1376782.64 ±2113942.94
DAAs regimens	
SOF + DAC 24 weeks	111 (52.11%),
SOF/ LDV 24 weeks	18 (8.45%),
SOF/ VEL 24 weeks	5 (2.35%).
SOF + DAC + RBV 12 weeks	74 (34.74%),
SOF/ LDV + RBV 12 weeks	5 (2.35%).
Child score	7.2 ± 0.4
MELD score	13.74 ± 1.43
BE3A score, range	1 – 4
1	41 (19.3%)
2	69 (32.4%)
3	82 (38.5%)
4	21 (9.9%)

Table (2): Biochemical parameters follow-up during DAAs without RBV (n=134)

		COMP.	Differences	Paired Test	
	Mean ± SD		Mean ± SD	T	P-value
AST Before	69.42±25.75				
AST After 1 M	48.11± 15.30	**B-1M**	21.31 ± 30.69	8.475	**<0.001***
AST After 2 M	47.49± 13.94	**B-2M**	22.09 ± 53.82	4.993	
AST After 3 M	40.45± 10.96	**B-3M**	29.13 ± 28.71	12.344	
AST After 4 M	38.59± 11.31	**B-4M**	31.21±30.05	12.601	
AST After 5 M	37.57± 10.48	**B-5M**	31.90±28.81	13.379	
AST After 6 M	36.92± 12.28	**B-6M**	32.25±29.08	13.400	
ALT Before	59.10± 19.07				
ALT After 1 M	35.78± 14.64	**B-1M**	23.32±24.46	11.640	**<0.001***
ALT After 2 M	33.43± 11.91	**B-2M**	25.87±23.13	13.610	
ALT After 3 M	30.43± 1082	**B-3M**	28.87±22.19	15.829	
ALT After 4 M	30.102± 9.85	**B-4M**	29.42±21.49	16.597	
ALT After 5 M	29.44± 9.95	**B-5M**	30.08±21.18	17.216	
ALT After 6 M	27.20± 9.09	**B-6M**	32.08±21.17	18.308	
Hb Before	10.81± 0.70				
Hb After 1 M	10.77± 0.78	**B-1M**	0.03±0.91	0.433	0.666
Hb After 2 M	10.81± 0.82	**B-2M**	-0.003±1.04	-0.032	0.975
Hb After 3 M	10.84± 0.90	**B-3M**	-0.034±1.09	-0.430	0.668
Hb After 4 M	10.82± 0.81	**B-4M**	-0.009±1.03	-0.104	0.917
Hb After 5 M	10.81± 0.79	**B-5M**	-0.005±0.91	-0.063	0.950
Hb After 6 M	10.914± 0.78	**B-6M**	-0.111±0.93	-1.445	0.151
Platelet Before	87.55± 15.25				
platelet After 1 M	89.839± 20.90	**B-1M**	-2.29±24.28	-1.150	0.252
platelet After 2 M	88.88± 23.14	**B-2M**	-1.16±26.33	-0.537	0.592
platelet After 3 M	94.26± 22.84	**B-3M**	-6.54±26.09	-3.050	0.003*
platelet After 4 M	93.33± 22.49	**B-4M**	-5.52±26.57	-2.521	0.013*
platelet After 5 M	94.49± 20.73	**B-5M**	-6.68 ± 24.45	-3.312	0.001*
platelet After 6 M	95.021± 23.11	**B-6M**	-7.30±26.38	-3.341	0.001*
WBCs Before	5.26± 1.78				
WBCs After 1 M	5.12± 1.42	**B-1M**	0.13±0.91	1.804	0.073
WBCs After 2 M	5.07± 1.13	**B-2M**	0.20±1.14	2.095	0.068
WBCs After 3 M	5.35± 1.13	**B-3M**	-0.08±1.42	-0.669	0.505
WBCs After 4 M	5.39± 0.98	**B-4M**	-0.12± 1.64	-0.908	0.365
WBCs After 5 M	5.29± 0.90	**B-5M**	-0.02±1.86	-0.136	0.892
WBCs After 6 M	5.42± 0.92	**B-6M**	-0.17± 1.99	-1.002	0.318

B: baseline, M: month, ALT: alanine aminotransferase, AST: aspartate aminotransferase, WBCs: white blood cells, Hb: hemoglobin.

Table (3): Biochemical parameters follow-up during DAAs plus RBV (n= 79

Parameters		COMP.	Paired Test		
	Mean± SD		Mean	T	P-value
ALT Before	54.89 ± 22.51				
ALT After 2 W	39.34 ± 13.58	**B-2W**	15.54 ±17.95	8.483	**<0.001***
ALT After 1 M	38.40 ± 14.29	**B-1M**	16.49 ±17.26	9.359	
ALT After 1.5 M	38.40 ± 14.29	**B-1.5M**	16.49 ±17.26	9.359	
ALT After 2 M	34.72 ± 10.90	**B-2M**	20.36 ± 20.45	9.655	
ALT After 2.5 M	34.72 ± 10.90	**B-2.5M**	20.36 ± 20.45	9.655	
ALT After 3 M	33.47 ± 10.39	**B-3M**	22.33 ± 20.40	10.440	
AST Before	66.41 ± 17.36				
AST After 2 W	54.65 ± 12.30	**B-2W**	11.76 ± 18.29	6.299	
AST After 1 M	54.38 ± 12.48	**B-1M**	12.03 ± 18.24	6.46	
AST After 1.5 M	54.38 ± 12.48	**B-1.5M**	12.03 ± 18.24	6.46	
AST After 2 M	49.16 ± 10.64	**B-2M**	17.40 ± 18.34	9.20	**<0.001***
AST After 2.5 M	49.16 ± 10.64	**B-2.5M**	17.40 ± 18.34	9.20	
AST After 3 M	49.53 ± 10.32	**B-3M**	17.35 ± 19.89	8.32	
Hb Before	12.23± 0.51				
Hb After 2 W	11.68 ± 0.45	**B-2W**	0.54 ± 0.36	14.82	**<0.001***
Hb After 1 M	11.39 ± 0.54	**B-1M**	0.84 ± 0.47	17.70	
Hb After 1.5 M	11.02 ± 0.58	**B-1.5M**	1.21 ± 0.49	23.81	
Hb After 2 M	10.89 ± 0.57	**B-2M**	1.34 ± 0.51	25.48	
Hb After 2.5 M	10.75 ± 0.57	**B-2.5M**	1.48 ± 0.54	25.59	
Hb After 3 M	10.59 ± 0.56	**B-3M**	1.65 ± 0.66	23.94	
Platelet Before	86.10 ± 14.82				
Platelet After 2 W	83.60 ± 16.14	**B-2W**	2.50 ± 6.45	3.80	<0.001*
Platelet After 1 M	84.24 ± 15.10	**B-1M**	1.87 ± 8.54	2.14	0.035*
Platelet After 1.5 M	84.287± 15.61	**B-1.5M**	1.96 ± 8.74	2.17	0.033*
Platelet After 2 M	85.93 ± 15.87	**B-2M**	0.32 ± 8.14	0.38	0.705
Platelet After 2.5 M	87.68 ± 18.74	**B-2.5M**	-1.10 ± 12.48	-0.84	0.405
Platelet After 3 M	89.82 ± 17.86	**B-3M**	-3.07 ± 12.79	-2.29	**0.025***
WBCs Before	6.36 ± 2.05				
WBCs After 2 W	6.10 ± 1.77	**B-2W**	0.26 ± 2.61	0.96	0.340
WBCS After 1 M	6.17 ± 1.55	**B-1M**	0.19 ± 1.62	1.164	0.247
WBCs After 1.5 M	6.07 ± 1.69	**B-1.5M**	0.25 ±2.05	1.161	0.248
WBCs After 2 M	6.19 ± 1.65	**B-2M**	0.13 ± 1.70	0.757	0.451
WBCs After 2.5 M	6.17 ± 1.65	**B-2.5M**	0.15 ± 1.72	0.866	0.389
WBCs After 3 M	6.29 ± 1.81	**B-3M**	0.06 ± 2.21	0.269	0.789
Total Bilirubin Before	1.74 ± 0.25				
Bilirubin After 2 W	1.94 ± 0.28	B-2W	-0.20 ± 0.22	-8.601	**<0.001***
Bilirubin After 1 M	1.95 ± 0.23	B-1M	-0.21 ± 0.23	-8.973	
Bilirubin After 1.5 M	1.92 ± 0.27	B-1.5M	-0.18 ± 0.30	-5.885	
Bilirubin After 2 M	1.88 ± 0.242	B-2M	-0.14 ± 0.29	-4.781	
Bilirubin After 2.5 M	1.92 ± 0.285	B-2.5M	-0.19 ± 0.34	-5.230	
Bilirubin After 3 M	1.96 ± 0.26	B-3M	-0.23 ± 0.34	-6.416	
Indirect bilirubin Before	0.98 ± 0.29				
Indirect bilirubin After 2 W	1.06 ± 0.22	B-2W	-0.086 ± 0.27	-2.964	0.004*
Indirect bilirubin After 1 M	1.08 ± 0. 20	B-1M	-0.10 ± 0.27	-3.636	<0.001*
Indirect bilirubin After 1.5 M	1.03 ± 0.23	B-1.5M	-0.06 ±	-1.889	0.062
Indirect bilirubin After 2 M	1.01 ± 0.21	B-2M	-0.04 ± 0.32	-1.164	0.248
Indirect bilirubin After 2.5 M	1.03 ± 0.21	B-2.5M	-0.06 ±0.32	-1.627	0.107
Indirect bilirubin After 3 M	1.10 ± 0.24	B-3M	-0.13 ± 0.36	-3.448	0.001*

B: baseline, M: month, ALT: alanine aminotransferase, AST: aspartate aminotransferase, WBCs: white blood cells, Hb: hemoglobin. T: total

Follow-up at 12 weeks after EOT & 24 weeks after SVR:

***Impact of DAAs on clinical & laboratory parameters:** The number of ascetic patients was significantly decreased from 58 (27.23%) before treatment to 37 (17.37%) at 24 weeks after SVR only (p-value = 0.020) **(Table 4).**

AFP, bilirubin, and INR were significantly decreased at both 12 weeks after EOT & 24 weeks after SVR & while serum albumin was significantly increased only at 24 weeks after SVR (3.08 ± 0.195 versus 3.04 ± 0.22) (p-value = 0.014). MELD score was significantly decreased from 13.74 ±1.43 before treatment to 13.14 ± 1.28 & 13.02 ±1.27 at 12 weeks after EOT & at 24 weeks after SVR respectively (p-value < 0.001), so number of patients with MELD <15 was significantly increased from 151 to 185 & 189 at 12 weeks after EOT and 24 weeks after SVR respectively (p-value <0.001) **(completed Table 4).**

Table (4): Follow-up at 12 weeks after EOT (SVR) & 24 weeks after SVR

		Baseline	**12 weeks after EOT (SVR)**	**24 weeks after SVR**
		N (%)	**N (%)**	**N (%)**
MELD class	**<15**	151 (70.89%)	185 (86.85%)	189 (88.73%)
	>15	62 (29.11%)	28 (13.15%)	24 (11.27%)
COMP.	**B & 12 weeks**		**B & 24 weeks**	
P-value	<0.001*		<0.001*	
Ascites	**No**	155 (72.77%)	163 (76.53%)	176 (82.63%)
	Yes	58 (27.23%)	50 (23.47%)	37 (17.37%)
COMP.	**B & 12 weeks**		**B & 24 weeks**	
P-value	0.436		0.020*	
HE (grade 1-2)	**No**	209 (98.12%)	207 (97.18%)	208 (97.65%)
	Yes	4 (1.88 %)	6 (2.82 %)	5 (2.35%)
COMP.	**B & 12 weeks**		**B& 24 weeks**	
P-value	0.749		1.000	
HCC	**No**	213 (100 %)	211 (99.06%)	209 (98.12%)
	Yes	0 (0.00)	2 (0.94%)	4 (1.88%)
COMP.	**B & 12 weeks**		**B & 24 weeks**	
P-value	0.167		0.132	

Completed table (4)

	MELD			COMP.	Differences		Paired Test	
	Mean	**±**	**SD**		**Mean**	**SD**	**T**	**P-value**
Base	13.74	±	1.43					
12 weeks after EOT (SVR)	13.14	±	1.28	**B-12 weeks**	0.601	1.358	6.457	<0.001*
24 weeks after SVR	13.012	±	1.27	**B-24 weeks**	0.718	1.556	6.739	<0.001*
	Albumin			**COMP.**	**Differences**		**Paired Test**	
	Mean	**±**	**SD**		**Mean**	**SD**	**T**	**P-value**
Base	3.039	±	0.215					
12 weeks after EOT (SVR)	3.054	±	0.198	**B-12 weeks**	-0.015	0.184	-1.157	0.248
24 weeks after SVR	3.080	±	0.195	**B-24 weeks**	-0.041	0.241	-2.484	**0.014***
Time	**INR**			**COMP.**	**Differences**		**Paired Test**	
	Mean	**±**	**SD**		**Mean**	**SD**	**T**	**P-value**
Before	1.580	±	0.186					
12 weeks after EOT (SVR)	1.534	±	0.152	**B-12 weeks**	0.046	0.168	4.012	**<0.001***
24 weeks after SVR	1.534	±	0.175	**B-24 weeks**	0.046	0.230	2.942	**0.004***
Time	**Bilirubin**			**COMP.**	**Differences**		**Paired Test**	
	Mean	**±**	**SD**		**Mean**	**SD**	**T**	**P-value**
Baseline	1.782	±	0.284					
12 weeks after EOT (SVR)	1.699	±	0.275	**B-12 weeks**	0.083	0.248	4.895	**<0.001***
24 weeks after SVR	1.700	±	0.303	**B-24 weeks**	0.082	0.335	3.563	**<0.001***
Time	**AFP**			**COMP.**	**Differences**		**Paired Test**	
	Mean	**±**	**SD**		**Mean**	**SD**	**T**	**P-value**
Baseline	8.593	±	3.654					
12 weeks after EOT (SVR)	6.665	±	2.238	**B-12 weeks**	1.928	2.727	10.320	**<0.001***
24 weeks after SVR	6.155	±	3.696	**B-24 weeks**	2.438	4.721	7.537	**<0.001***

AFP: Alfa-fetoprotein. B: baseline, HE: hepatic encephalopathy, CTP: Child-Turcotte-Pugh, MELD: Model for End-Stage Liver Disease, HCC: hepatocellular carcinoma, EOT: end of treatment, SVR: sustained virologic response

Impact of DAAs on CTP score at follow-up (Table 5)

There was a highly significant improvement in CTP score at 12 weeks after EOT, the number of CTP A, CTP B, and CTP C patients were 71 (33.3%), 141 (66.2%), 1 (0.47%) respectively so, we had 33.33% attained compensated CTP A.

There was a highly significant improvement in CTP score at 36 weeks after the start of DAAs, the number of CTP A, CTP B, and CTP C patients were 103 (48.36%), 109 (51.17%) and 1 (0.47%) respectively. So, we had 48.36 % attained compensated CTP A.

There was a highly significant improvement in CTP score at 24 weeks after SVR, the number of CTP A, CTP B, and CTP C patients were 119 (55.87%), 92 (43.2%), 1 (0.94%). So, we had 55.87 % attained CTP class A **(primary study outcome**).

Table (5): Impact of DAAs on CTP score at follow-up

Child	**Before**	**12 weeks after EOT (SVR)**	**36 weeks of treatment start**	**24 weeks after SVR**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Child A	0 (0.00)	71 (33.33)	103 (48.36)	119 (55.87)
Child B	213 (100)	141 (66.20)	109 (51.17)	92 (43.19)
Child C	0 (0.00)	1 (0.47)	1 (0.47)	2 (0.94)
Total	213 (100)	213 (100)	213 (100.00)	213 (100)
Chi-Square		**B-12 weeks**	**B-36 weeks**	**B - 24 weeks**
P-value		<0.001*	<0.001*	<0.001*

B: Baseline, EOT: end of treatment, SVR: sustained virologic response.

Comparison between improved (CTP A) and non-improved patients: At 36 weeks of treatment start, BMI, ALT, INR, ascites and BE3Ascore were the significant baseline factors for improvement to CTP A (**Table 6).** At multivariant analysis, a high baseline BE3A score was the only significant baseline predictor of improvement from CTP B to CTP A (OR = 2.07, 95% CI: 1.009-4.23, p-value = 0.05 **(Table 7).**

At 24 weeks after SVR, ALT, ascites, albumin, INR and BE3A score were the significant factors to attain CTP A **(Table 8).** At multivariant analysis, ALT was the only significant baseline predictor for improving from CTP B to CTP A (1.040 – 5.889 OR, 95% CI for OR, p = 0.040) **(Table 9).**

Table (6): Comparison between improved (CTP A) and non-improved patients at 36 weeks of treatment start

		CTP class at 36 weeks of start of treatment						Chi-Square	
		Non-Improved		Improved		Total			
		N	%	N	%	N	%	X^2	P-value
Age	**<60 Years**	82	74.55	74	71.84	156	73.24	0.198	0.656
	>60 Years	28	25.45	29	28.16	57	26.76		
Gender	**Male**	52	47.27	47	45.63	99	46.48	0.058	0.810
	Female	58	52.73	56	54.37	114	53.52		
BMI	**<25**	7	6.36	17	16.50	24	11.27	12.259	**0.002***
	25-30	50	45.45	58	56.31	108	50.70		
	>30	53	48.18	28	27.18	81	38.03		
ALT	**<60 U/L**	80	72.73	32	31.07	112	52.58	37.025	**<0.001***
	>60 U/L	30	27.27	71	68.93	101	47.42		
Albumin	**<2.8 g/dl**	9	8.18	3	2.91	12	5.63	2.778	0.096
	2.8-3.5 g/dl	101	91.82	100	97.09	201	94.37		
INR	**1.7-2.2**	25	22.73	45	43.69	70	32.86	10.594	**0.001***
	<1.7	85	77.27	58	56.31	143	67.14		
Bilirubin	**2-3 mg/dl**	33	30.00	31	30.10	64	30.05	0.000	0.988
	<2 mg/dl	77	70.00	72	69.90	149	69.95		
HE	**No**	107	97.27	102	99.03	209	98.12	0.891	0.345
	Yes	3	2.73	1	0.97	4	1.88		
Ascites	**No**	61	55.45	94	91.26	155	72.77	34.419	**<0.001***
	Yes	49	44.55	9	8.74	58	27.23		
MELD class	**<15**	79	71.82	72	69.90	151	70.89	0.095	0.758
	>15	31	28.18	31	30.10	62	29.11		
Platelet	**<100**	81	73.64	74	71.84	155	72.77	0.086	0.769
	>100	29	26.36	29	28.16	58	27.23		
BE3A score	**1**	35	31.82	6	5.83	41	19.25	52.599	**<0.001***
	2	47	42.73	22	21.36	69	32.39		
	3	25	22.73	57	55.34	82	38.50		
	4	3	2.73	18	17.48	21	9.86		

Table (7): Multivariate analysis of factors predicting the improvement to CTP class A at 24 weeks after SVR.

Baseline predictors	Odd ratio	95% CI for Odd ratio	P-value
BMI	0.73	0.42 -1.26	0.26
ALT	1.86	0.77- 4.47	0.17
INR	1.02	0.49 - 2.12	0.97
Ascites	0.71	0.24 - 2.15	0.55

BE3A score	2.07	1.009 - 4.23	**0.05***

Table (8): Comparison between improved (CTP A) and non-improved patients at 24 weeks after SVR

Baseline parameters		CTP class at 24 weeks After SVR						Chi-Square	
		Non-Improved		Improved (CTP A)		Total			
		N	%	N	%	N	%	X^2	P-value
Age	**<60 Years**	68	72.34	88	73.95	156	73.24	0.069	0.792
	>60 Years	26	27.66	31	26.05	57	26.76		
Gender	**Male**	41	43.62	58	48.74	99	46.48	0.554	0.457
	Female	53	56.38	61	51.26	114	53.52		
BMI	**<25**	8	8.51	16	13.45	24	11.27	5.750	0.056
	25-30	42	44.68	66	55.46	108	50.70		
	>30	44	46.81	37	31.09	81	38.03		
ALT	**<60 U/L**	70	74.47	42	35.29	112	52.58	32.323	**<0.001***
	>60 U/L	24	25.53	77	64.71	101	47.42		
Albumin	**<2.8 g/dl**	9	9.57	3	2.52	12	5.63	4.915	**0.027***
	2.8-3.5 g/dl	85	90.43	116	97.48	201	94.37		
INR	**1.7-2.2**	20	21.28	50	42.02	70	32.86	10.239	**0.001***
	<1.7	74	78.72	69	57.98	143	67.14		
Bilirubin	**2-3 mg/dl**	29	30.85	35	29.41	64	30.05	0.052	0.820
	<2 mg/dl	65	69.15	84	70.59	149	69.95		
HE	**No**	92	97.87	117	98.32	209	98.12	0.057	0.811
	Yes	2	2.13	2	1.68	4	1.88		
Ascites	**No**	49	52.13	106	89.08	155	72.77	36.181	**<0.001***
	Yes	45	47.87	13	10.92	58	27.23		
MELD class	**<15**	72	76.60	79	66.39	151	70.89	2.653	0.103
	>15	22	23.40	40	33.61	62	29.11		
Platelet	**<100**	68	72.34	87	73.11	155	72.77	0.016	0.900
	>100	26	27.66	32	26.89	58	27.23		
BE3A score	**1**	34	36.17	7	5.88	41	19.25	47.429	**<0.001***
	2	37	39.36	32	26.89	69	32.39		
	3	18	19.15	64	53.78	82	38.50		
	4	5	5.32	16	13.45	21	9.86		

Table (9): Multivariate analysis of factors predicting the improvement to CTP A at 24 weeks after SVR

Baseline predictors	Odd ratio (OR)	95% C.I of OR	P-value
ALT	2.48	1.04 - 5.89	**0.040***
Albumin	1.67	0.33 - 8.57	0.54
INR	1.008	0.48 -2.12	0.98
Ascites	0.39	0.14 -1.12	0.08
BE3A score	1.52	0.81- 2.87	0.19

The proportion of CTP A in relation to BE3A score: The responders (CTP A) were 6 patients (14.63%), 22 (31.88%), 57 (69.51%) and 18 (85.71%) with a BE3A score of 1, 2, 3 and 4 respectively **(Figure 2).**

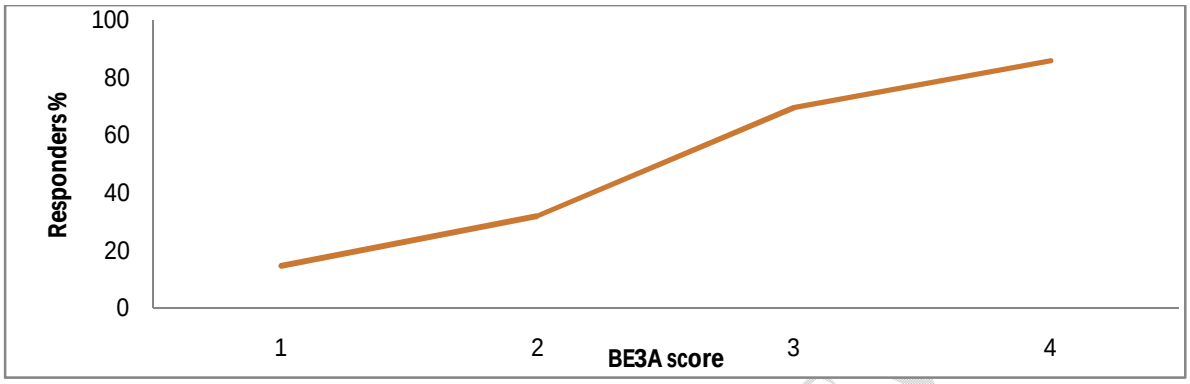

Fig. (2): The proportion of CTP A in relation to BE3A score at 36 weeks of treatment start.

Secondary study outcomes: SVR 12 was achieved in 97.33%. We had 33 dropped patients during study including 8 patients during DAAs and 25 patients during follow-up as shown in **(Figure 1**). Approximately, 49 patients had liver adverse events during follow-up (26 patients developed new onset ascites, 6 patients had developed HCC, 8 patients had more advanced CTP scores, 9 patients had new onset HE (grade 1-2). Also, 33 patients had tolerable side effects during DAA therapy, of them 13 patients had anemia, 9 patients had fatigue, 7 patients had headache and 4 patients had diarrhea.

Discussion:

The availability of SOF-based DAAs has led to a paradigm change in the treatment of HCV-related decompensated cirrhosis [5]. Achieving SVR is associated with a considerable improvement in CTP and MELD scores [6, 9]. Therefore, there was an urgent need to look for pretreatment predictors that associated with improvement to compensated CTP A cirrhosis. To determine how effective the treatment was in CTP B cirrhosis, we extended the follow-up period to 24 weeks after SVR.

We had (55.9 %) patients attained CTP A in the post-treatment follow-up period of 24 weeks after SVR (the primary endpoint of our study). The baseline ALT (> 60 IU/L), serum albumin (> 2.8 g/dl), INR (<1.7), absence of ascites, and high BE3A score were significantly associated with attaining CTP A.

By logistic regression analysis only ALT (> 60 IU/L) was the only significant predictor of attaining CTP A (OR = 2.48, 95% CI: 1.04 -5.89, p-value = 0.04). A higher baseline ALT was more likely to benefit from antiviral treatment suggesting the existence of active hepatocyte damage from HCV in decompensated patients which was comparable to HBV decompensated patients [13].

The BE3A score of our patients was ranged from 1 to 4**.** The number of CTP A patients was higher with higher BE3A score about 85.7% with BE3A score 4, 69.5% with BE3A score 3, 31.88% with BE3A score 2 and 14.63% with BE3A score 1 (figure 2). This was like ***El- Sherif et al*** who reported revealed that a BE3A score 3-4 has a 75% chance of achieving CTP A after DAAs [10]. Also, like ***Debnath et al*** who reported the number of responders was 25%, 43.75%, 93.75% and 100% with a BE3A score of 1, 2, 3 and 4 respectively [12].

At 36 weeks of treatment start, we had 48.36% attained CTP A. The baseline variables as BMI (<25), absence of ascites, ALT (> 60 IU/L) and a high BE3A score were the significant variables between improved (CTP A) and non-improved. At multivariate analysis, a high BE3A score was the only significant baseline predictor of attaining CTP A (OR = 2.07, 95% CI: 1.009-4.23, p = 0.05).

A near similar finding reported by ***El-Sherif et al.*** who retrospectively studied 502 CPT class B and 120 CPT class C patients and reported that 31.6 % improved to CTP A [10]. The proportion of improved patients after DAAs in our study was higher than their result (48.36% versus 31.6%).

This high chance of improvement in our study may be due to 78.4% of our patients were CTP B7, whereas their patients were advanced cirrhosis (CTP B & C). ***Debnath et al.*** studied 62 decompensated patients (55 CTP B & 7 CTP C) and reported a significant improvement to CTP A by 54.83 % at 36 weeks of starting DAAs [12]. Also, ***Ahmed et al.*** studied 32 CTP B patients and reported that 68.7% attained CTP A [14]. This discrepancy between their and our results may be due to the different numbers of studied patients.

During DAAs, we reported a significant decrease in ALT, AST, and a significant increase in platelet count during DAAs until EOT. Our findings were comparable to those published by ***Gentile et al. and Bakr et al.*** [15, 16]. The improved enzymes could be related to the effect of DAAs in reduction of HCV induced hepatic inflammation and hepatic damage. The increased platelets agreed with ***Badawi et al. Chen et al.*** [17, 18] which might be related to decrease in portal pressure, platelet aggregation in hepatic tissues, and platelet destruction. The decreased Hb and increased bilirubin was reported only with DAAs plus RBV, which was like ***Ahmed et al.*** who reported that low Hb was a prevalent adverse effect of RBV in decompensated patients and more anemia in CTP-B patients treated with DAAs plus RBV [14]. This result was due to low RBV clearance in decompensated cirrhosis leading to RBV overexposure and increased toxicity [19].

Serum bilirubin & INR were significantly decreased at both 12 weeks after EOT (SVR) & 24 weeks after SVR compared to baseline. Serum albumin was significantly increased at 24 weeks after SVR compared to baseline. This was like studies that reported improvements in total bilirubin and albumin at follow-up after achieving SVR [16, 20]. Contrary studies by ***Gentile et al and Hanafy et al*** who reported not a significant decrease in INR after achieving SVR over time in decompensated cirrhosis [15,21].

Serum AFP was significantly decreased at both 12 weeks after EOT (SVR) & 24 weeks after SVR, which was in accordance with many studies [23,24]. HCC developed in 2 patients at 12 weeks after EOT (SVR) and 4 patients at 24 weeks after SVR without any significance which was consistent with a large Egyptian study conducted by ***Shiha et al.***

who found that HCC incidence decreased in HCV-related decompensated patients who achieved SVR [25]. The number of ascetic patients was significantly decreased at 24 weeks after SVR compared to baseline which might be attributed to DAAs' ability to reduce further hepatic decompensation and portal hypertension that reported by many studies [20, 22].

Finally, HCV DAAs were effective in CTP B with high SVR12 (97.33%) which explained by high potency of DAAs, and most of the studied patients (78.4%) were CTP B7**.** This result was like those of ***Debnath et al***. who reported that SVR12 was 98.6% in CTP B [12]. Also, ***Gentile et al. and Ahmed et al***. reported that the SVR12 was 95.5 % & 93.75 % respectively [14,15]. This result was against ***El-Sherif et al, El Raziky et al. and Pageaux et al.*** who reported that SVR12 was 85%, 82.9% and 88 % respectively **[10, 26, 27].** The lower SVR rates in the opposite studies could be explained by the difference in the studied populations, as most of our patients were early CTP B whereas theirs were CTP B & CTP C, as well as altered DAAs metabolism, reduced drug delivery by shunting and altered DAAs uptake due to more impaired hepatic synthetic function in late CTP B & CTP C.

Conclusion:

About 55.9 % had improved to CTP class A and a high baseline ALT (> 60 IU/L) was the significant predictor of attaining CTP A at 24 weeks after SVR. The number of CTP A patients was higher with higher baseline BE3A score which was the significant predictor of attiring CTP A at 36 weeks of treatment start. HCV DAAs were effective, safe, and associated with significant improvements in liver function with high rates of improvement of CTP B to CTP A cirrhosis so, we recommend early treatment of CTP B cirrhosis who have a high baseline ALT > 60 IU/L or a high baseline BE3A score as they have a high chance of improvement after HCV DAAs and these patients become at a low priority for LT or even delisted.

Ethical Approval and Consent

The study was ethically approved by Ethical Committee of Faculty of Medicine, Tanta University (Approval code 32987/3/19). A written informed consent was obtained, and all patients had code number to insure their privacy.

Limitations of this study: Some limitations that we had met in our study were COVID-19 precautionary measures which restricted many patients' commitment to therapy and follow-up, small sample size and short duration follow-up that limited to 24 weeks after SVR. Furthermore, the study was conducted only on CTP B cirrhotic patients according to Egyptian protocol for HCV treatment so, our results cannot be generalized to CTP C cirrhosis. So, further studies are still needed to overcome these limitations.

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